Molecular Basis and Clinical Overview of McLeod Syndrome Compared With Other Neuroacanthocytosis Syndromes: A Review

Roulis, Eileen ; Hyland, Catherine ; Flower, Robert ; Gassner, Christoph ; Jung, Hans H ; Frey, Beat M

Abstract: Importance McLeod syndrome, encoded by the gene XK, is a rare and progressive disease that shares important similarities with Huntington disease but has widely varied neurologic, neuromuscular, and cardiologic manifestations. Patients with McLeod syndrome have a distinct hematologic presentation with specific transfusion requirements. Because of its X-linked location, loss of the XK gene or pathogenic variants in this gene are principally associated with the McLeod blood group phenotype in male patients. The clinical manifestation of McLeod syndrome results from allelic variants of the XK gene or as part of a contiguous gene deletion syndrome involving XK and adjacent genes, including those for chronic granulomatous disease, Duchenne muscular dystrophy, and retinitis pigmentosa. McLeod syndrome typically manifests as neurologic and cardiologic symptoms that evolve in individuals beginning at approximately 40 years of age. Observations Diagnosis of McLeod syndrome encompasses a number of specialties, including neurology and transfusion medicine. However, information regarding the molecular basis of the syndrome is incomplete, and clinical information is difficult to find. The International Society of Blood Transfusion has recently compiled and curated a listing of XK alleles associated with the McLeod phenotype. Of note, McLeod syndrome caused by structural variants as well as those cases diagnosed as part of a contiguous gene deletion syndrome were previously classified under a singular allele designation. Conclusions and Relevance This review discusses the clinical manifestations and molecular basis of McLeod syndrome and provides a comprehensive listing of alleles with involvement in the syndrome published to date. This review highlights the clinical diversity of McLeod syndrome and discusses the development of molecular tools to elucidate genetic causes of disease. A more precise and systematic genetic classification is the first step toward correlating and understanding the diverse phenotypic manifestations of McLeod syndrome and may guide clinical treatment of patients and support for affected and carrier family members. This review provides a knowledge base for neurologists, hematologists, and clinical geneticists on this rare and debilitating disease.

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CONCLUSIONS AND RELEVANCE This review discusses the clinical manifestations and molecular basis of McLeod syndrome and provides a comprehensive listing of alleles with involvement in the syndrome published to date. This review highlights the clinical diversity of McLeod syndrome and discusses the development of molecular tools to elucidate genetic causes of disease. A more precise and systematic genetic classification is the first step toward correlating and understanding the diverse phenotypic manifestations of McLeod syndrome and may guide clinical treatment of patients and support for affected and carrier family members. This review provides a knowledge base for neurologists, hematologists, and clinical geneticists on this rare and debilitating disease.

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Supplemental content

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The Story of Hugh McLeod and an Interesting Case of McLeod Syndrome

The Kx antigen and, subsequently, the syndrome associated with loss of the antigen were discovered as a result of changes in antigenicity of the Kell blood group. McLeod syndrome (MLS) was first identified in an otherwise healthy 25-year-old male student at Harvard dental school, Hugh McLeod, through his novel Kell erythrocyte antigen profile, which was obtained as part of an unconsented screening survey undertaken in 1961 among incoming students.[1-3] McLeod's red blood cells manifested with evenly depressed Kell antigens and the loss of a public antigen, termed Kx. Initially, the Kx antigen was thought to be an antigen of the Kell blood group. The first description of antibody against the Kx antigen (anti-Kx) was published by Marsh et al[2] in 1975 in a study of young patients with chronic granulomatous disease and their relatives. The lack of Kx antigen was therefore linked to chronic granulomatous disease. However, the absence of chronic granulomatous disease symptoms in McLeod puzzled researchers because he also lacked Kx antigen on his red blood cells. We now understand that the reason for the absence of Kx antigen in McLeod was that his condition had a genetic basis that was considerably different from that of the patients in the survey by Marsh et al.[2]

McLeod continued his dental practice, despite progression of MLS symptoms, to the age of 64 years, and he died when he was 69 years of age.[4] The variant responsible for the McLeod phenotype was identified as a 13–base pair (bp) deletion at position 938-951 in the *XK* gene (OMIM: 314850) that resulted in a premature stop at amino acid 336.[5]

Discovery of the *XK* Gene

The Kx antigen is encoded by the *XK* gene at the p21.1 region of the X chromosome (accession numbers: NG_007473.2 [genomic], NM_021083.3 [transcript], LRG_812 [locus reference genomic identifier]). The *XK* gene spans a locus of 42 501 bp with 3 exons for a total coding region of 1335 bp, and the resulting mature protein has 444 amino acids. The chromosomal region associated with McLeod syndrome was located by comparative probe mapping of 10 samples from patients with MLS to a series of specifically defined clones spanning a region between the 2 loci known to cause Duchenne muscular dystrophy and chronic granulomatous disease.[6] The gene responsible for the McLeod phenotype was defined years later using radiolabeled cosmid probes, which uncovered a number of large nucleotide deletions in patients with MLS. The candidate gene was identified as *XK* and displayed a tissue distribution and expression pattern consistent with MLS.[7]

McLeod syndrome and chronic granulomatous disease were initially thought to be genetically linked, but we now know that the genes associated with chronic granulomatous disease (*CYBB*) (OMIM: 300481) and MLS (*XK*) are separate but in close proximity (<50 kbp apart) on the X chromosome. The deletion of all or part of both genes is often associated with a contiguous gene deletion syndrome, with larger deletions often involving genes associated with Duchenne muscular dystrophy (*DMD*) (OMIM: 300377) and retinitis pigmentosa (*RPRG*) (OMIM: 300110). This finding indicates that the lack of Kx antigen and McLeod phenotype in the young patients with chronic granulomatous disease in the 1975 study by Marsh et al[2] was likely caused by contiguous gene deletion syndrome rather than specific genetic variants confined to the *XK* locus, as was the case for McLeod.

Serologic Presentation of Kx Antigen and MLS

Hematologic findings diagnostic for MLS are distinct and separate the presentation of MLS from that of other diseases under the neuroacanthocytosis umbrella.[8] The patient should present with an absence of Kx antigen and reduced expression of Kell blood group antigens demonstrated using a panel of human anti-Kx and monoclonal anti-Kell antibodies. This initial presentation facilitates a diagnostic algorithm for confirmatory testing of MLS. The presence of the *KEL* gene (OMIM: 613883) should be confirmed using polymerase chain reaction or other molecular methods to differentiate from the Kell-null phenotype.[9] The patient should be assessed for alloantibodies against the high-frequency antigen Kx, the high-frequency Kell antigen Km (also known as KEL20), and the presence of a compensated hemolytic state. The level of biochemical markers associated with hemolysis, such as lactate dehydrogenase and haptoglobin, should be determined, and serum creatine kinase levels, which are usually elevated in patients with MLS with concentrations reaching 4000 U/L (to convert to microkatals per liter, multiply by 0.0167), should also be determined. The presence of red blood cell acanthocytes should be confirmed using phase-contrast microscopy.[8]

Neuroacanthocytosis and MLS

McLeod syndrome is part of the spectrum of neuroacanthocytosis syndromes, which are defined as progressive neurodegenerative diseases that affect mainly basal ganglia, including nucleus caudatus and putamen, in association with red blood cell anomalies, such as acanthocytosis.[8-12] Major representatives of neuroacanthocytosis sydromes with vastly overlapping clinical features are the autosomal-recessive choreoacanthocytosis (ChAc) and the X-linked MLS. Although panthothenate-kinase–associated neurodegeneration and Huntington disease–like disorder may rarely be associated with red blood cell acanthocytosis, these syndromes markedly differ from ChAc and MLS with respect to age of onset and mode of inheritance. Clinical features of the neuroacanthocytosis syndromes are outlined in the **Table**.

Autosomal-recessive choreoacanthocytosis and MLS share many common phenotypic features, such as choreatic movement disorder, cognitive impairment and associated psychiatric disorders, seizures, and neuromuscular involvement with elevated creatine kinase levels, myopathy, and peripheral neuropathy associated with diminished or abolished deep-tendon reflexes.[10,13] These neuromuscular manifestations may widely differ in severity, ranging from isolated elevation of creatine kinase levels to disabling muscular weakness and atrophy. Because serum transaminase levels may also be elevated in patients with MLS,[14] patients have been misdiagnosed with hepatopathy. However, some patients with MLS have hepatosplenomegaly, most probably resulting from an increased red blood cell turnover caused by elevated red blood cell clearance in the context of the acanthocytic changes.[5,15]

Several neurologic manifestations in patients with ChAc, such as tongue and lip biting, tongue protrusion dystonia, head drops, parkinsonism, and truncal dystonia, were formerly believed to be specific for this disorder. However, recent reports describe these

Table. Clinical Presentation and Molecular Basis of Neuroacanthocytosis Syndromes

Characteristic	Chorea-Acanthocytosis	McLeod Syndrome	Huntington Disease-Like 2	Pantothenate Kinase-Associated Neurodegeneration
Gene	*VPS13A*	*XK*	*JPH3*	*PANK2*
Protein	Chorein	XK	Junctophilin-3	Pantothenate kinase-2
Inheritance	Autosomal recessive	X-linked	Autosomal dominant	Autosomal recessive
Acanthocytes	+++	+++	+/−	+/−
Cellular compartment	Cytoplasm	Membrane	Cytoplasm	Mitochondria
Membrane proteins affected	Band3/adducin, actin junctional complex	Band3/4.1R complex, actin junctional complex	None	None
Red blood cell phenotype	Unaffected	Weak Kell antigens, Kx antigen absent	Unaffected	Unaffected
Serum creatine kinase level, U/L	300-3000	300-3000	Normal	Normal
Neuroimaging	Striatal atrophy	Striatal atrophy	Striatal and cortical atrophy	"Eye of the tiger" sign in the globus pallidus
Age of onset, y	20-30	25-60	20-40	Childhood
Chorea	+++	+++	+++	−
Other movement disorders	Feeding and gait dystonia, tongue and lip biting, parkinsonism	Vocalizations, parkinsonism	Dystonia, parkinsonism	Dystonia, parkinsonism, spasticity
Seizures	Generalized, partial-complex	Generalized	None	None
Neuromuscular manifestations	Areflexia, weakness, atrophy	Areflexia, weakness, atrophy	None	None
Cardiac manifestations	None	Atrial fibrilliation, malignant arythmias, dilative cardiomyopathy	None	None

Abbreviations: −, absent; +, present; +++, maximum presence.

SI conversion: To convert serum creatine kinase to microkatals per liter, multiply by 0.0167.

manifestations in patients with MLS, which suggests a widely shared clinical spectrum between ChAc and MLS.[16,17] The major distinguishing clinical features of MLS are mode of inheritance, red blood cell immunophenotype, and cardiologic involvement—mainly dilated cardiomyopathy and arrhythmias.

Phenotypic Variability

McLeod syndrome may exhibit a considerable phenotypic variability, even within the same family, with regard to the age at onset, the presenting symptoms, the development of additional symptoms, and the course of the disease.[18] In a series of patients with MLS, 3 had MLS detected as a result of donating blood, 3 presented with variable psychiatric disorders, 2 reported muscular weakness and atrophy or epileptic seizures, and only 1 had a choreatic movement disorder at the disease onset.[4]

Although the rarity of the disorder does not allow a conclusive genotype-phenotype correlation, available data suggest that missense mutations in the *XK* gene tend to lead to less pronounced neurologic and neuromuscular symptoms with a later onset than *XK* variants that cause truncation or nonexpression of the XK protein.[19,20] This would be consistent with a residual physiologic activity in female carriers of *XK* missense mutations.[14,21] However, all available clinical reports are consistent with a full penetrance of MLS in men, albeit possibly at an older age and possibly with nondisabling neurologic or neuromuscular symptoms. These considerations are important in the context of genetic counseling of patients with MLS and family members at risk of disease.

Clinical Diagnosis of MLS

The variable presentation of Xp21.1. mutations[18,19,22,23] together with late onset of clinical symptoms make the diagnosis of MLS challenging. Diagnosis is almost exclusively restricted to male, middle-aged patients who exhibit a progressive chorea syndrome with the exclusion of other pathologies such as Huntington disease, Wilson disease, ChAc, and *c9orf72*-related disorders.[8,24,25] Neurologic presentation of symptoms is highly variable, although choreatic movement disorder; dystonia; cognitive impairment with premature dementia; psychiatric disorders including depression, bipolar disorder, and obsessive-compulsive disorder; and personality changes are common.[16,17,26] Areflexia or hyporeflexia are characteristic as are elevated creatine kinase levels and red blood cell abnormalities ranging from overt acanthocytosis to elevated rates of hyperchromic red blood cells in automated hematologic analysis. Serologic test results that indicate an absence of the Kx antigen are used to confirm diagnosis. Among blood donors with MLS, the absence of the Kx antigen may be recognized many years before clinical manifestation of symptoms and may even lead to an early diagnosis of MLS in asymptomatic blood donors.[3,19] This is important to note for hematologists because this finding implies the probable development of neurologic and/or neuromuscular symptoms later in life and the necessity for neurogenetic counseling of these blood donors.

In addition to mutations at the *XK* locus, large X-chromosomal deletions involving *XK* and its neighboring loci may lead to contigu-

ous gene deletion syndrome,[27] the clinical manifestation of which is dictated by deleted genes both upstream and downstream of *XK*, such as *DMD*, *CYBB*, and *RPRG*. Patients may experience Duchenne muscular dystrophy, chronic granulomatous disease, or retinitis pigmentosa, respectively. Other coaffected genes at Xp21.1 with poorly defined biologic functions, such as *MRXS17*, *BCMP1*, *MAGEB16*, and *PRRG1*, may modify the clinical presentation of contiguous gene deletion syndrome. If several genes are affected, disease symptoms may develop sequentially over time, ultimately leading to a dismal outcome,[28] although the clinical presentation and diagnosis of contiguous gene deletion syndrome typically occurs at an early age.[28,29] Treatment options for MLS and contiguous gene deletion syndrome are limited to symptomatic care to prevent secondary complications, such as amelioration of dystonia and choreatic movement disorder,[30] treatment of muscular degeneration,[31,32] and treatment of infectious complications in chronic granulomatous disease.[33]

Women with Manifestations of MLS

As an X-linked neuroacanthocytosis syndrome, MLS is overwhelmingly confined to male patients. Lyonization (or X-inactivation) of the defective gene results in a normal phenotype or, rarely, weakened clinical presentation in women. It is possible that severe MLS in women could occur as the result of a compound heterozygosity, although to our knowledge, this is yet to be reported.[34]

Of interest, in the only case of a woman with confirmed severe MLS to our knowledge, the proband was heterozygous for a 1-bp deletion in exon 2 in the *XK* gene (268delT terminating at AA129). It was shown that severely skewed lyonization resulted in inactivation of the normal *XK* gene in all tissues, including the brain. The patient developed seizures at 50 years of age, with gradual progression of neurologic symptoms including chorea and cognitive impairment before her death at 60 years of age.[14,21] Both of the patient's sons had MLS, with neurohematologic symptoms manifesting from their early to mid-20s before their deaths at the age of 31 years. The patient's sister and niece each exhibited mild neurologic symptoms (lower limb chorea and ankle areflexia) with variable presentation of Kell antigens, whereas the skew of lyonization ranged from slightly skewed in the sister to completely normal in the niece. Age-related skew of lyonization has been reported in female patients who present with progressive X-linked disorders,[35,36] which could explain the difference in skew between affected women. All family members with the variant, including heterozygotes, had hematologic profiles—acanthocytosis and elevated creatine kinase levels—that were consistent with MLS to varying degrees.

Biochemistry and Cell Biology of XK

In the red blood cell membrane, XK is a 10-transmembrane protein that forms a heterodimer with the Kell glycoprotein via the disulfide bond at XK^{Cys347}-$Kell^{Cys72}$, as shown in **Figure 1**A. The XK-Kell dimer is part of the membrane multiprotein complex subunit 4.1, which also contains Band3 glycoprotein, glycophorin C, Rh protein/Rh-associated glycoprotein, and Duffy protein[38] (Figure 1B). The membrane multiprotein complex cytoskeleton network controls the blood cell discocyte shape and determines cell deformability, among other properties.[39,40] Similar to other multipass-membrane transport proteins, XK may be an important gate keeper for transmembrane exchange of electrolytes and nutrients.[41] It has been shown that absence of the XK-Kell membrane complex alters erythrocyte homeostasis of divalent cations,[42,43] which may explain premature hemolysis of red blood cells in individuals with MLS by impairment of Ca^{2+}-activated K+ channels (Gardos channels).[44] Lipid imbalance between the inner and outer red blood cell membrane leaflets leads to acanothcytic deformation of the red blood cell membrane. The absence of XK protein in the membrane leads to diminished levels of phosphatidylserine in the inner leaflet, which causes shrinkage of the membrane, interfering with transmembrane metabolite transport.[45,46]

In many nonerythroid tissues, the XK protein and Kell protein are expressed independently from each other, and in most tissue, including the brain and other neuronal tissue, only *XK* is translated.[47] The XK protein has been shown to have a pivotal role in organogenesis, cellular structure, and subcellular electrolyte and nutrient exchange, accounting for the multisystemic deficiency phenotype, which includes neurologic, neuropsychiatric, neuromuscular, and cardiologic manifestations.[4,5,48] As a matter of course, all manifestations attributable to *XK* alone may be drawn only from observations in (and experiments involving) individuals with mutations limited to the *XK* locus who do not exhibit a contiguous gene deletion syndrome.

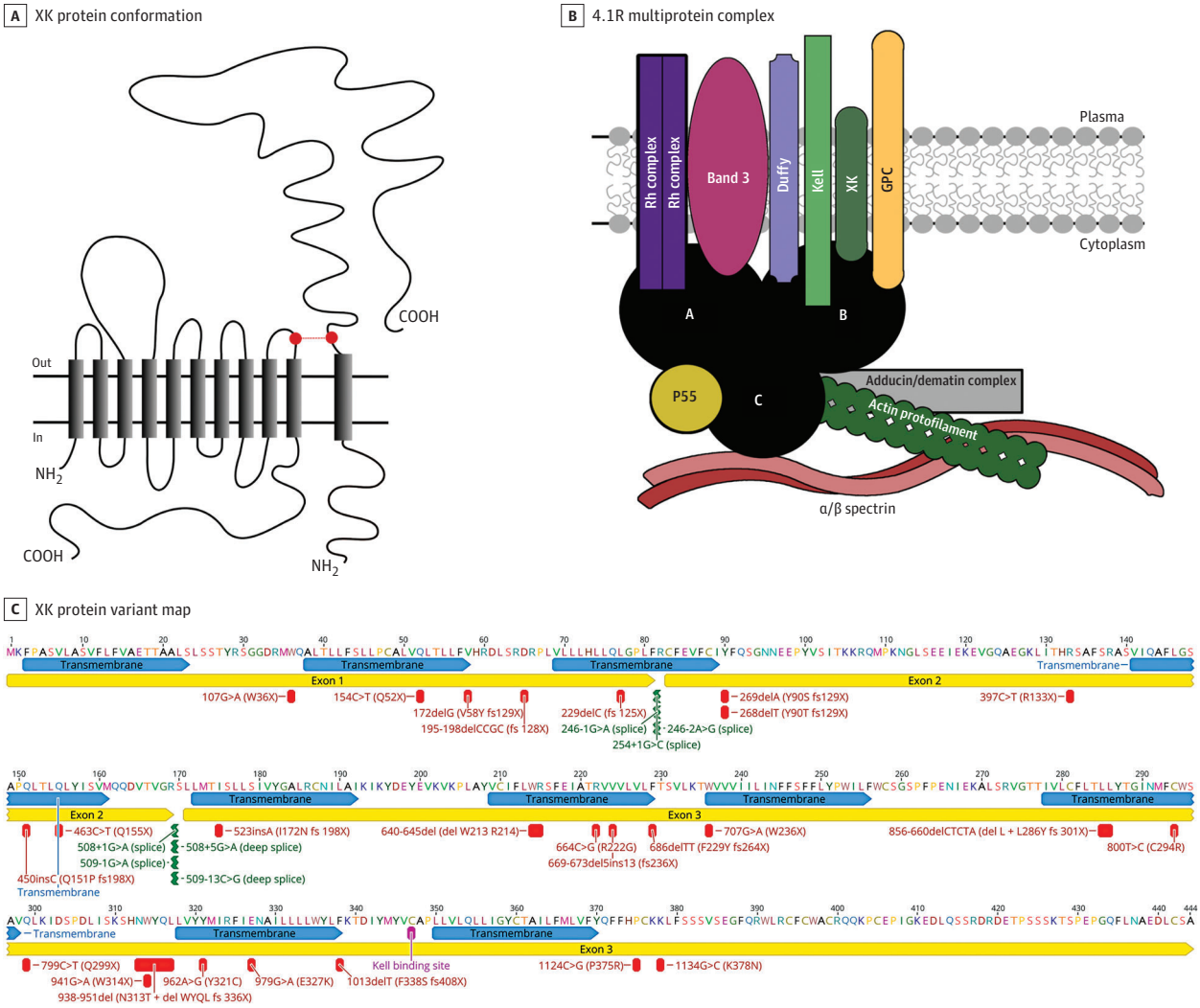
Genetic Classification of *XK* Alleles and the Molecular Basis of MLS

The International Society of Blood Transfusion (ISBT) recognizes the XK protein and Kx antigen as an independent blood group system, defined as number 019 of the currently recognized 36 blood group systems. At present, the data described in the *XK* allele database comprise the most complete repository of variants with an associated McLeod phenotype.

The Kx antigen, encoded by the native XK protein, is designated as the reference allele defined as *XK*01*. No other antigens have been defined in this system. The *XK* gene shows 8.2 variants per kilobase coding sequence, thereby ranking as one of the most conserved blood group genes, second only to Chido/Rodgers, encoded by *C4A* and *C4B*, with 5.5 and 4.4 variants per kilobase, respectively.[49] In addition to the variants described in the ISBT database, an additional 66 variants coding for changes in *XK*, including 1 nonsense variant, have been reported in the dbSNP (single-nucleotide polymorphism database). It is unknown whether any of these variants have an associated MLS phenotype.

Until this review, 29 variant alleles associated with the McLeod phenotype were listed in the ISBT database and defined as *XK*N* from 01 to 29, with *N* indicating null. Review of the literature shows that this is now an underestimate and that at least 56 variant *XK* alleles have been described in conjunction with neurogenic or hematologic *XK* phenotypes. The variants are subdivided into 2 groups: variants residing within *XK* (39 alleles) or whole gene deletions, including contiguous gene deletions involving the *XK* gene (17 alleles). Consequently, and in conjunction with the ISBT working party, we have compiled a comprehensive listing of all described MLS and neurogenically associated variants involving the *XK* gene.[50] This listing provides neurologists, clinical geneticists, and transfusion specialists with a reference to further investigate the

Figure 1. XK-Kell Complex and Amino Acid Variation in the McLeod Phenotype



XK is a 444–amino acid, 10-transmembrane protein that forms a dimer with the Kell protein in the 4.1R complex of the red blood cell membrane multiprotein complex. A, Ten-transmembrane conformation of the XK protein, with its disulphide linkage at XK^{Cys347}-$Kell^{Cys72}$ in red. B, Main components of the 4.1R-dependent multiprotein complex in the red blood cell membrane. The 4.1R protein, which anchors the red cell membrane components, is depicted with its 3-lobe structure: A, B, and C. Defects in components of the 4.1R complex can lead to instability and deformity of the red blood cell membrane, such as the presentation of acanthocytosis seen in McLeod syndrome (MLS). C, The XK protein, showing the arrangement of exons, locations of transmembrane segments, and locations of amino acid changes associated with the MLS phenotype. The XK protein variant map was generated with Geneious 11.0.5 (Biomatters Limited) using human genome release Hg19 p13.7.[37] COOH indicates carboxyl group; GPC, glycophorin C protein.

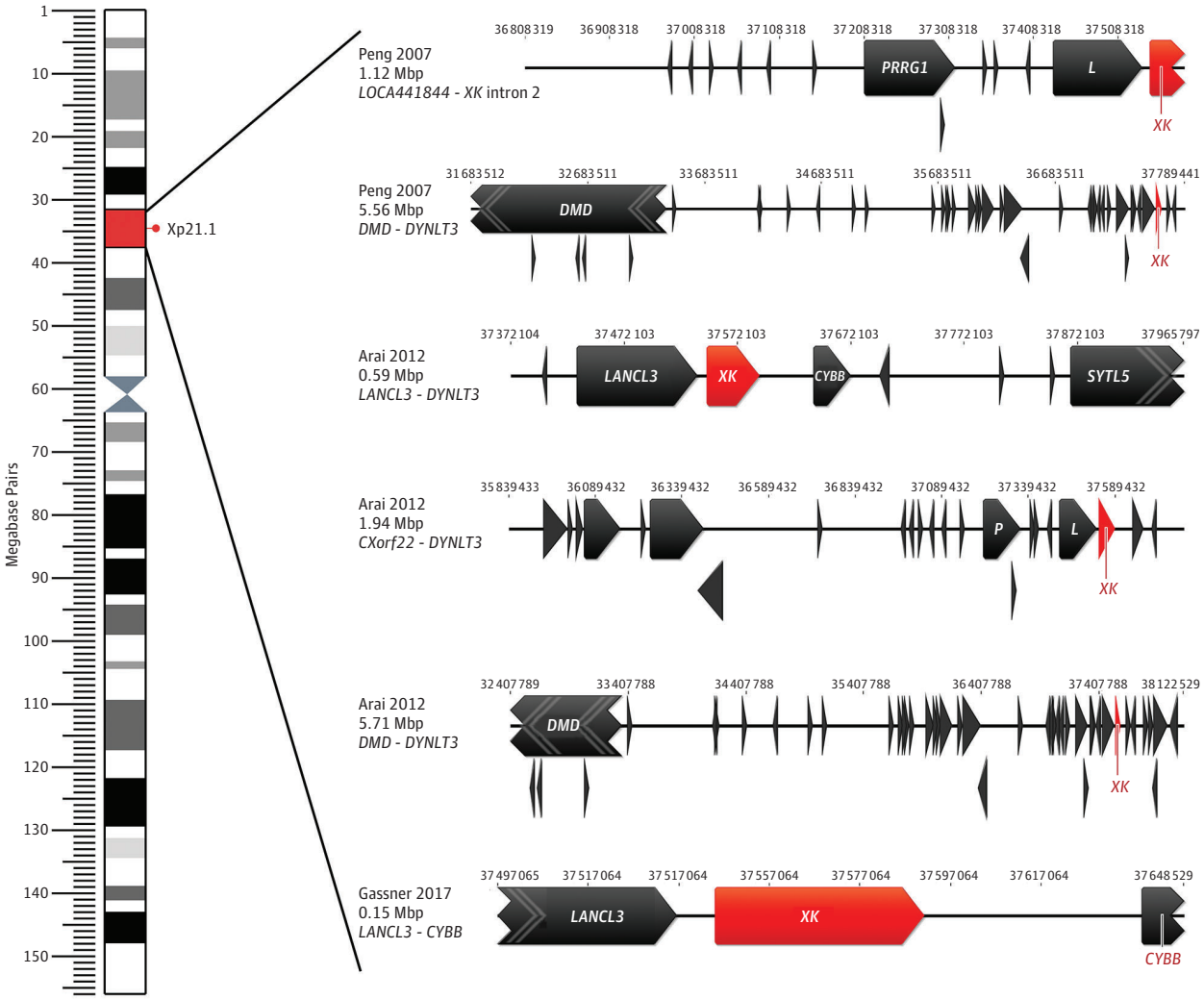
molecular basis of MLS and report findings of novel alleles or deletions in individuals presenting with a McLeod phenotype.

Review of the *XK*N* Allelic Variant Group

The majority of *XK*N* alleles consist of variants in 1 of the 3 exons or splice site loci of the *XK* gene. A summary of the *XK* allele variants derived from the ISBT database is presented in eTable 1 in the Supplement. The location of single-nucleotide variants and indels associated with the MLS phenotype are depicted in Figure 1C.

Many of these variants are single-nucleotide polymorphisms or small deletions that result in amino acid changes or frameshifts and early termination of the XK protein. Only 2 single-nucleotide insertions with a McLeod phenotype association are noted.[51-53] Nucleotide variants resulting in amino acid substitutions presumably disrupt transmembrane helices and change conformation for the mature protein within the cell membrane. A splice site mutation 13 bp downstream of the exon 3 acceptor site has been associated with psychiatric pathology (schizophrenia) and acanthocytosis in patients but was not described as presenting with a McLeod phenotype.[54] Only 3 of the *XK* variants with an MLS association have been listed in the dbSNP database (rs numbers 28933690, 104894954, and 104894953); 5 variants are listed with a ClinVar accession, whereas 2 splice site variants have listed ExAC/GnomAD population-level frequencies. Most alleles are reported from a single patient or family grouping. However, 5 alleles have been reported in more than 1 study—for instance, the R133X vari-

Figure 2. Scale and Variability of Deletions in Contiguous Gene Deletion Syndromes With McLeod Syndrome (MLS) Phenotype



Six contiguous gene deletions in the Xp21.1 locus with clearly defined nucleotide breakpoints are shown. The deletions involve *XK*, with clinical presentation of MLS. The deletions span from 0.15 megabase pairs (Mbp) to 5.71 Mbp and involve 3 to more than 15 genes. The scale depicts the size and number of nucleotides in the X-chromosome. The gene maps were generated with Geneious 11.0.5 (Biomatters Limited) using human genome release Hg19 p13.7.[37] *L*, *LANCL3*; and *P*, *PRRG1*.

ant has been reported in 3 separate studies from apparently unrelated kindreds[5,55,56] (these cases are outlined in eTable 2 in the Supplement).

Review of the *XK*N.01* Series With Contiguous Gene Deletions

To date, 17 whole gene or contiguous gene deletions that include *XK* have been published (these are outlined in eTable 3 in the Supplement). Because of the molecular technologies available at the time that many of the older deletions were defined, breakpoints for these deletions are not precisely mapped. Given the rarity of whole gene deletions and contiguous gene deletions involving *XK*, the probability that the same deletion will be tabulated more than once is unlikely except in cases in which descent can be confirmed from familial studies. The suballeles are listed on the basis of the accuracy of locus and nucleotide discrimination: those that were characterized using older methods, such as microscopic examination or karyotyping and probe deletion analyses,[57,58] and those for which descriptions of deletions are determined with breakpoints to the nucleotide level. **Figure 2** illustrates the range of the deletions associated with MLS and contiguous gene deletion syndromes for the 6 cases in which exact breakpoints are defined.

Whole genome sequencing now allows researchers to more easily determine the nucleotide breakpoints involved in contiguous gene deletion syndrome and MLS. In addition, polymerase chain reaction and Sanger sequencing targeting splice site and exonic regions or stepwise partitioned polymerase chain reaction analysis of *XK* and flanking regions are still used for the discovery of mutations responsible for the McLeod blood group phenotype.[27,59] In the case of *XK* deletions, the stepwise partitioning method can be used to determine exact nucleotide breakpoints without the requirement for whole genome sequencing.[27] With the introduction of third-

generation sequencing technologies, such as the BioRad SMRT and Oxford Nanopore ION systems, the detection and analysis of very large-scale deletions will become easier and the characterization of breakpoints easier to define. A more precise and systematic genetic classification is the first step toward correlating and understanding the diverse phenotypic clinical manifestations of MLS to guide management strategies.

Treatment and Future Directions

The importance of early and correct diagnosis, along with the role that hematology laboratories can play in this early detection, has been reviewed elsewhere.[9] Currently, treatment of patients with MLS and associated contiguous gene deletion syndromes involves monitoring and amelioration of symptoms. Dopamine antagonists and the dopamine depletory drug tetrabenazine are given to ameliorate the choreatic movement disorders, whereas treatment of psychiatric problems, cardiac abnormalities, and seizures is based on clinical findings and whether contiguous genes with additional clinical presentations are involved. Regardless, long-term and continuous multidisciplinary support is needed for affected individuals and their families, including genetic counseling of affected and potentially affected male relatives.

The rare blood group phenotype characteristic for patients with MLS, in lacking the Kx antigen, presents challenges. Any patient carrying the McLeod immunophenotype because of either MLS or contiguous gene deletion syndrome and requiring transfusion support requires the care and support of specialist transfusion institutions. In such cases, the immunohematologic and molecular workup is demanding, and the rarity of compatible blood products often requires interinstitutional or international collaboration for provision of compatible units.[8] In any case of transfusion requirement, Kx+ transfusions should be avoided for both male and female patients carrying a McLeod phenotype. Autologous banked donations are the most suitable transfusion practice if feasible.

Treatment options using allogeneic stem cell transplant therapies have been reported with some success.[60] A young man with MLS and chronic granulomatous disease who had developed antibodies to Kx and Kell after a red blood cell transfusion received a successful allogeneic stem cell transplant at 14 years of age, with observed complete chimerism and engraftment after 10-month follow-up.[61,62] Unfortunately, there is no guarantee that a successful transplant will prevent late onset of neurologic and neuromuscular symptoms or cardiac complications associated with inherited Xp21.1 defects.

Recent studies have demonstrated promising results with the use of nonhomologous end-joining recombination using RNA-guided CRISPR/Cas9 nucleases in repairing short indel and frameshift variations in the chronic granulomatous disease gene *CYBB*, with less success in repairing single-nucleotide variants leading to nonsense and missense mutations. Although the technology is still in its infancy, these therapies may be directly translatable to other monogenic hematopoetic blood disorders, such as MLS.[63,64] In addition, the use of targeted insertion of therapeutic transgenes into defined viral integration sites will allow for alteration of the patient's own stem cells for transplantation.[65] Of note, the morphologically, functionally, and structurally altered red blood cells in *XK* mutation carriers may provide an easily accessible cellular substrate to determine the pathobiologic features of Xp21.1 mutations and to discover new potential therapeutic strategies for improvement of multisystem manifestations of MLS.[66]

Conclusions

McLeod syndrome is a progressive, debilitating X-linked neurohematologic disorder that is caused by variation in the *XK* gene, resulting in truncation of the mature XK protein or changes in transmembrane conformation and structure within the red blood cell membrane and other tissues. McLeod syndrome can also present as part of a contiguous gene deletion syndrome caused by a whole or partial gene deletion, including deletion of adjacent genes such as *CYBB, DMD,* and *RPGR*. It can occur in individuals 20 years of age or older, whereas neurologic, neuromuscular, and cardiologic manifestations vary widely and occur late in a patient's life. Information on the molecular basis of MLS and associated gene deletion syndromes has previously been diffuse and widely distributed. We collected and elaborated on the molecular basis of MLS to provide a reference base for clinicians.

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